Synthesis of Highly Functionalized Fluorinated Cispentacin Derivatives

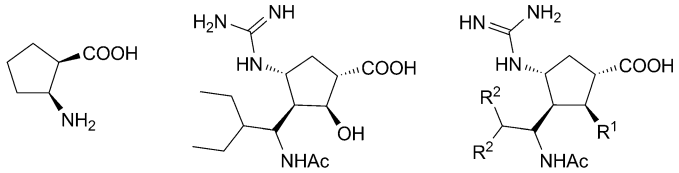
by **Melinda Nonn**[a])[b]), **Loránd Kiss**[a]), **Mikko M. Hänninen**[c]), **Reijo Sillanpää**[c]), and **Ferenc Fülöp***[a])[b])

[a]) Institute of Pharmaceutical Chemistry, University of Szeged, HU-6720, Eötvös 6
[b]) Stereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, HU-6720 Szeged, Eötvös 6
[c]) Department of Chemistry, University of Jyväskylä, FI-40014, Jyväskylä

Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Fluorinated highly functionalized cispentacin derivatives were synthetised starting from an unsaturated bicyclic β-lactam through C=C bond functionalization *via* the dipolar cycloaddition of a nitrile oxide, isoxazoline opening, and fluorination by OH/F exchange.

Introduction. – As a result of their biological potential, cyclic β-amino acids are of considerable importance in medicinal chemistry. As conformationally restricted derivatives, they are building blocks for the construction of biologically active peptides [1][2]. They include cispentacin (**1**), an important potent antifungal [1a][1b]. Multisubstituted aminocyclopentanecarboxylic acids such as Peramivir (**2**) and related analogs **3** (R^1 = H, OH; R^2 = Et, Pr) exhibit strong antiviral properties [3].



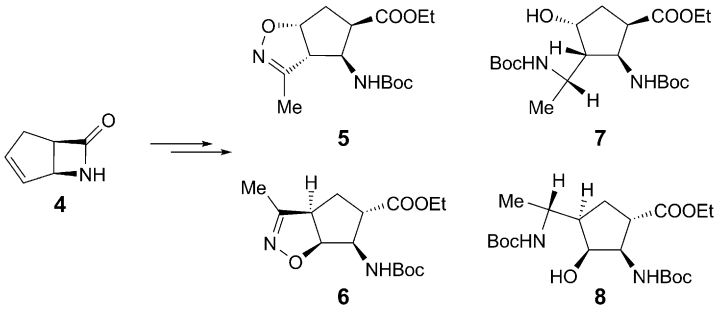
1 **2** **3**

Fluorinated α- and acyclic β-amino acids comprise an expanding area of research, with increasing impact in both chemistry and biochemistry. They are valuable in medicinal chemistry as enzyme inhibitors, antitumour agents, or antibiotics [4][5]. Only a small number of fluorinated cyclic β-amino acids have been prepared so far, this being particularly true for the five-membered derivatives [6].

We recently reported the synthesis of highly functionalized cispentacin stereoisomers **7** and **8** from bicyclic β-lactam **4** by means of the regio- and stereoselective 1,3-dipolar cycloaddition of a nitrile oxide (acetonitrile *N*-oxide) to ethyl *cis*- and *trans*-2-aminocyclopentene-3-carboxylates, followed by the stereoselective opening of the isoxazoline ring (*Scheme 1*) [7].

Results and Discussion. – Our current aim was to synthesize highly functionalized regio- and stereoisomers of F-containing five-membered cyclic β-amino acid deriva-

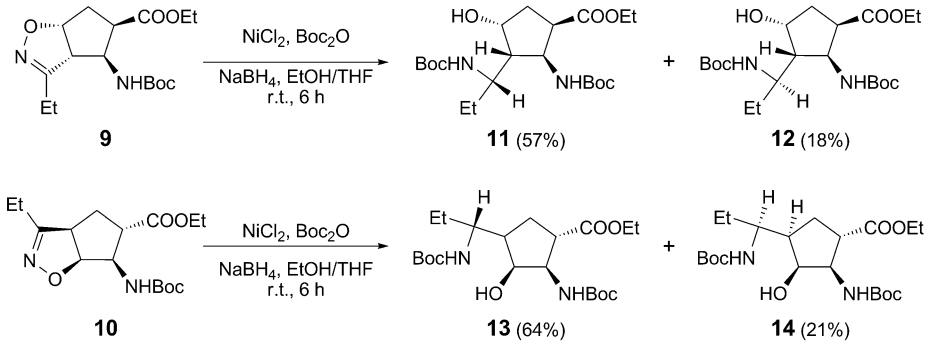
Scheme 1



tives from bicyclic β-lactam **4** through selective transformation of its C=C bond by the dipolar cycloaddition of a nitrile oxide, followed by reductive isoxazoline opening and H/F exchange.

Accordingly, novel OH-containing, multifunctionalized β-aminocyclopentanecarboxylates were prepared by reductive ring opening of the isoxazoline skeleton of **9** and **10** [8] (*Scheme 2*). In contrast to our earlier experiments on Me-substituted compounds (*cf. Scheme 1*) [7], the reductive isoxazoline opening of Et-substituted *cis*- and *trans*-isoxazoline-fused derivatives **9** and **10** under similar experimental conditions, with $NaBH_4$ in the presence of $NiCl_2$ in EtOH/THF, did not prove to be 100% stereoselective. Both transformations furnished two diastereoisomers, **11** (*Fig. 1*) and **12**, or **13** and **14**, in a ratio of 3 : 1, the major products, **11** and **13**, respectively, resulting from H attack on the isoxazoline from the same face of the carbamate (*Scheme 2*; for several related transformations, see [3]). The products **11** + **12** and **13** + **14** were separated and isolated by column chromatography on SiO_2.

Scheme 2



New multifunctionalized hydroxylated cispentacin analogs containing a longer alkyl chain were next prepared by cycloaddition of the nitrile oxide formed from 2-ethylbutyraldehyde oxime in the presence of *N*-chlorosuccinimide (NCS; *Huisgen*'s conditions) to ethyl *cis*- and *trans*-2-aminocyclohexenecarboxylates, **15** and **18**,

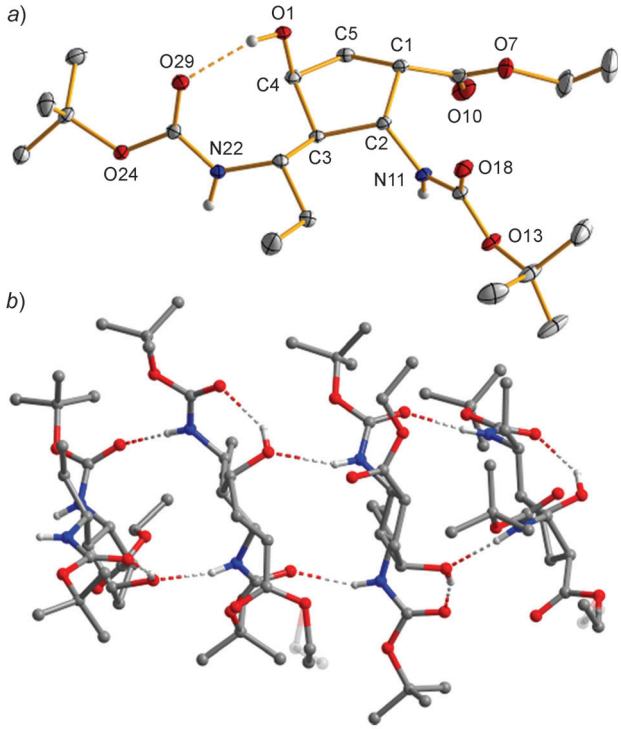


Fig. 1. a) *Molecular structure of compound* **11**. Only one of two similar molecules in the asymmetric unit is presented. b) *Ball-and-stick model of* **11** *showing inter- and intramolecular H-bonds.* Thermal ellipsoids have been drawn at 30% probability level, and the C–H H-atoms are omitted for clarity.

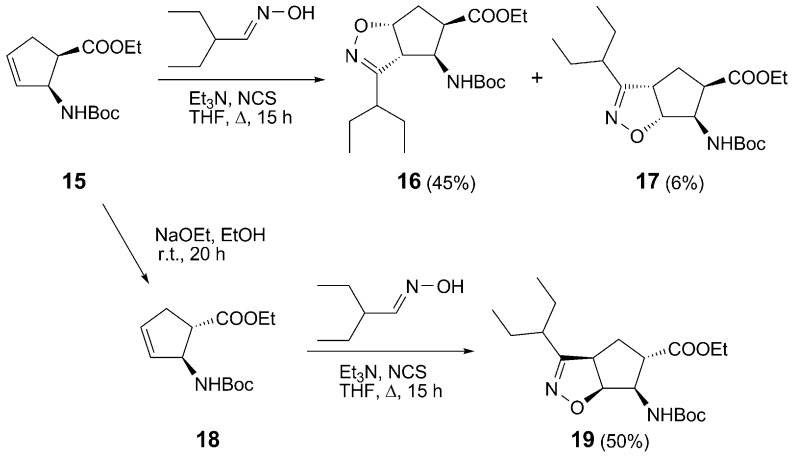
respectively (*Scheme 3*). The cycloaddition to **15** gave isoxazoline-fused amino ester regioisomers **16**/**17** in a ratio of 7.5 : 1 (*Scheme 3*), the major product containing the O-atom of the isoxazoline skeleton farther from the carbamate group (for analogous transformations, see [8a]). The products were separated by chromatography. Similarly as with other nitrile oxides [8b], the cycloaddition to the *trans* counterpart **18** selectively afforded only cycloadduct **19** (*Scheme 3*).

Analogously to **9** and **10**, the reductive ring openings of isoxazoline-fused *cis*- and *trans*-amino esters **16** and **19**, respectively, with $NaBH_4/NiCl_2$ each furnished two products, **20** (*Fig. 2*; the H_2O adduct of the compound)/**21**, or **22**/**23**, respectively, in a ratio of 2 : 1 and 3 : 1, which were separated by column chromatography (*Scheme 4*).

Introduction of a F-atom in the skeleton of the major isomers of the synthesized highly-functionalized cispentacin derivatives possessing a OH substituent was achieved through H/F exchange with *Deoxo-Fluor*® (= bis(2-methoxyethyl)aminosulfur trifluoride) as reagent.

Fluorination of **7**, **11**, and **20** in dry toluene at 0° for 2 h afforded the corresponding fluorinated compounds with inversion, **24a**–**24c**, and the elimination products **25a**–**25c**, respectively (for analogous experimental results, see [6a][6b] and ref. cit. therein; *Scheme 5*), which were separated by column chromatography. No experimental

Scheme 3



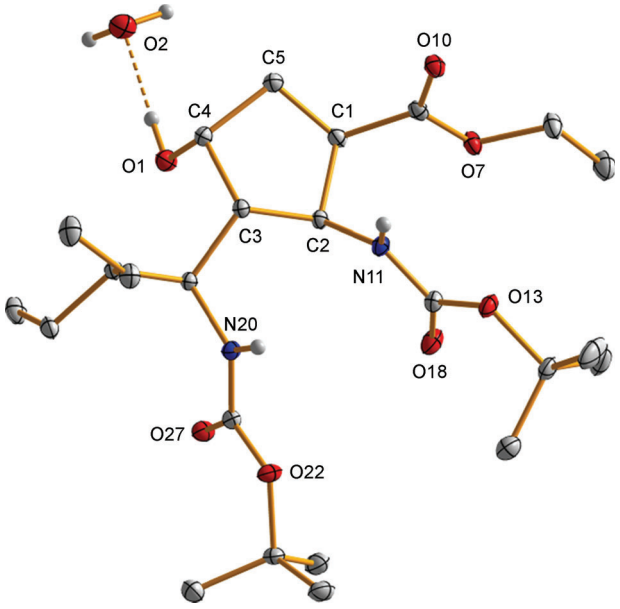
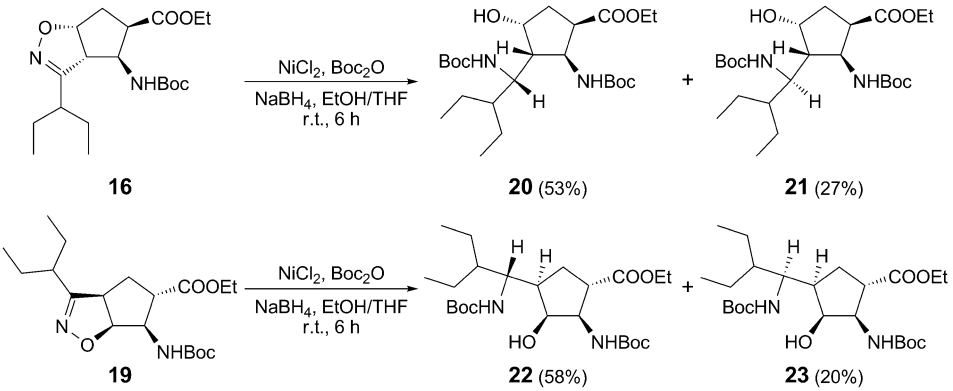


Fig. 2. *Molecular structure of compound* **20**·H_2O. Thermal ellipsoids have been drawn at 30% probability level, and the C–H H-atoms are omitted for clarity.

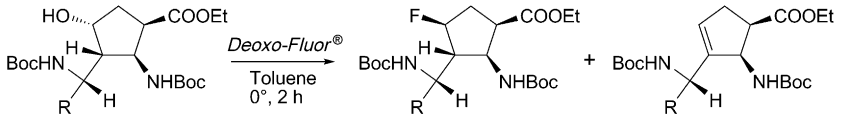
conditions were found under which the large amounts of elimination products could be avoided.

Under similar conditions, fluorination of the *trans* counterparts **8**, **13**, and **22** provided the required fluorinated products **26a** and **26b**, unfortunately again together with large quantities of elimination products **27a**–**27c**, respectively (*Scheme 6*).

Scheme 4

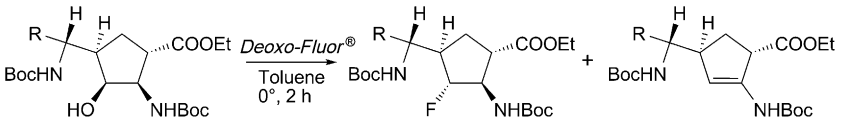


Scheme 5



	R	Yield [%]		R	Yield [%]
7 R = Me	**24a**	Me 24		**25a**	Me 45
11 R = Et	**24b**	Et 30		**25b**	Et 43
20 R = Et_2CH	**24c**	Et_2CH 28		**25c**	Et_2CH 27

Scheme 6



	R	Yield [%]		R	Yield [%]
8 R = Me	**26a**	Me 26		**27a**	Me 48
13 R = Et	**26b**	Et 15		**27b**	Et 39
22 R = Et_2CH	**26c**	Et_2CH 0		**27c**	Et_2CH 58

To summarize, highly functionalized fluorinated β-aminocyclopentanecarboxylate regio- and stereoisomers containing multiple stereogenic centers were synthesized from β-aminocyclopentenecarboxylates through the 1,3-dipolar cycloaddition of nitrile oxides and reductive ring opening of the isoxazoline skeleton, followed by H/F exchange. These products may be regarded not only as fluorinated cispentacin derivatives, but as precursors for the preparation of β-amino acid-modified peramivir analogs.

We are grateful to the *Hungarian Research Foundation* (OTKA No. NK81371 and K100530) for financial support.

Experimental Part

General. The chemicals were purchased from *Aldrich*. The solvents were used as received from the supplier. M.p.: *Kofler* apparatus. NMR Spectra: *Bruker DRX 400* spectrometer, chemical shifts, δ, in ppm rel. to TMS as internal standard, with $CDCl_3$ as solvent. MS: *Finnigan MAT 95S* spectrometer. Elemental analyses: *Perkin-Elmer CHNS-2400 Ser II* elemental analyzer.

Synthesis of 2-Ethylbutyraldehyde Oxime (=*(1*E*)-2-Ethyl*-N-*hydroxybutan-1-imine*). To a soln. of 2-ethylbutyraldehyde (=2-ethylbutanal; 50 mmol) in EtOH (50 ml), dry pyridine (150 mmol), and $NH_2OH \cdot HCl$ (50 mmol) were added, and the mixture was stirred under reflux for 7 h. The mixture was then concentrated under reduced pressure, and the crude residue was purified by column chromatography (CC) on SiO_2 (hexane/AcOEt) to give (1*E*)-2-ethyl-*N*-hydroxybutan-1-imine.

General Procedure for the Synthesis of Isoxazoline-Fused β-Aminocyclopentanecarboxylates. To a soln. of amino ester **15** or **18** (19.6 mmol) in THF (70 ml), (1*E*)-2-ethyl-*N*-hydroxybutan-1-imine (118 mmol), Et_2NH (19.6 mmol), and *N*-chlorosuccinimide (=1-chloropyrrolidine-2,5-dione; 78.4 mmol) were added, and the mixture was stirred at r.t. for 48 h. The mixture was then diluted with AcOEt (75 ml), washed with H_2O (3×20 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by CC (SiO_2; hexane/AcOEt to give **16**/**17** and **19**).

General Procedure for Isoxazoline Ring Opening. To a soln. of dihydroisoxazol **9**, **10**, **16**, or **19** (1.46 mmol) in 10 ml of EtOH/THF 3 :1 (*v*/*v*), $NiCl_2$ (2.92 mmol) and Boc_2O (2.92 mmol) were added. After stirring for 10 min, $NaBH_4$ (2.92 mmol) was added in portions. The mixture was stirred at r.t. for 5 h, and the reaction was then quenched by the addition of H_2O (5 ml). The mixture was filtered through *Celite* pad, and the filtrate was concentrated under reduced pressure. The residue was diluted with AcOEt (30 ml), washed with H_2O (3×10 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The products **11**/**12**, **13**/**14**, **20**/**21**, and **22**/**23** were purified and separated by CC (SiO_2; hexane/AcOEt).

General Procedure for the Synthesis of F-Containing β-Aminocyclopentanecarboxylates. To a soln. of hydroxy compounds **7**, **8**, **11**, **13**, **20**, or **22** (0.5 mmol) in dry toluene (10 ml), *Deoxo-Fluor*® soln. (50% in toluene, 0.6 mmol) was added at 0° under Ar. The mixture was stirred at 0° for 2 h, and the mixture was then diluted with AcOEt, washed with sat. $NaHCO_3$ soln. (3×10 ml), followed by H_2O (2×10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt)to furnish **24a**–**24c**, **25a**–**25c**, **26a** and **26b**, and **27a**–**27c**.

*Ethyl (1*R**,2*S**,3*S**,4*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-4-hydroxycyclopentanecarboxylate* (**11**). White solid. Yield: 57%. R_f (hexane/AcOEt) 0.24. M.p. 95–96°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 7.36, Me); 1.30 (*t*, *J* = 7.2, Me); 1.45 (*s*, ^{t}Bu); 1.49 (*s*, ^{t}Bu); 1.94–2.16 (*m*, 2 CH_2); 3.34–3.65 (*m*, H–C(1)); 3.79–3.89 (*m*, H–C(3)); 4.12–4.30 (*m*, H–C(2), CH, CH_2O); 4.44–4.55 (*m*, H–C(4)); 5.26–5.37 (br. *s*, NH); 5.61–5.72 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.9; 13.7; 27.9; 28.0; 28.4; 36.4; 43.8; 50.1; 50.3; 53.8; 60.3; 72.9; 79.3; 79.6; 155.2; 157.3; 174.9. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 58.55, H 8.92, N 6.49.

*Ethyl (1*R**,2*S**,3*S**,4*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*R**)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-4-hydroxycyclopentanecarboxylate* (**12**). White solid. Yield:18%. R_f (hexane/AcOEt 2 :1) 0.33. M.p. 125–127°. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.97 (*t*, *J* = 7.2, Me); 1.28 (*t*, *J* = 7.1, Me); 1.43 (*s*, ^{t}Bu); 1.48 (*s*, ^{t}Bu); 1.65–1.89 (*m*, CH_2); 1.96–2.18 (*m*, CH_2); 3.50–3.61 (*m*, H–C(1)); 3.66–3.77 (*m*, H–C(3)); 4.06–4.27 (*m*, CH, H–C(2); CH_2O); 4.38–4.49 (*m*, H–C(4)); 4.58–4.72 (br. *s*, 2 NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.0; 13.8; 25.3; 27.9; 35.4; 45.6; 50.9; 51.9; 56.6; 60.2; 71.3; 78.9; 79.5; 154.4; 156.7; 174.1. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 59.12, H 8.02, N 6.60.

*Ethyl (1*R**,2*S**,3*R**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-3-hydroxycyclopentanecarboxylate* (**13**). White solid. Yield: 64%. R_f (hexane/AcOEt) 0.57. M.p. 216–217°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (*t*, *J* = 7.4, Me); 1.25–1.33 (*m*, Me); 1.44 (*s*, ^{t}Bu); 1.49 (*s*, ^{t}Bu); 1.76–2.38 (*m*, 2 CH_2); 2.47–2.62 (*m*, H–C(1)); 2.76–2.96 (*m*, H–C(4)); 3.10–3.19 (*m*, H–C(2)); 3.68–3.80 (*m*, CH); 4.10–4.24 (*m*, CH_2O); 4.28–4.38 (br. *s*, NH); 4.42–4.47 (*m*, H–C(3)); 5.01–5.25 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.3; 11.1; 27.0; 28.1; 32.4; 33.2; 45.2; 52.3; 50.8; 54.1;

58.8; 72.1; 77.0; 154.5; 156.5; 175.4. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 58.57, H 8.91, N 6.49.

*Ethyl (1*R**,2*S**,3*R**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*R**)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-3-hydroxycyclopentanecarboxylate* (**14**). Brownish oil. Yield: 21%. R_f (hexane/AcOEt) 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (*t*, *J* = 7.6, Me); 1.25–1.33 (*m*, Me); 1.45 (*s*, ^{t}Bu); 1.50 (*s*, ^{t}Bu); 1.81–2.15 (*m*, 2 CH_2); 2.24–2.36 (*m*, H–C(4)); 2.74–2.86 (*m*, H–C(1)); 3.69–3.82 (*m*, CH); 4.09–4.26 (*m*, H–C(2), H–C(3), CH_2O); 4.29–4.39 (br. *s*, NH); 5.03–5.20 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.0; 11.0; 27.9; 28.0; 31.1; 35.5; 45.2; 51.7; 51.1; 56.5; 60.1; 71.6; 78.1; 154.4; 155.5; 174.6. ESI-MS: 453 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 58.57, H 8.98, N 6.50.

*Ethyl (3a*R**,4*S**,5*R**,6a*R**)-4-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,2]oxazole-5-carboxylate* (**16**). Brownish oil. Yield: 45%. R_f (hexane/AcOEt) 0.72. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90–1.00 (*m*, 2 Me); 1.30 (*t*, *J* = 7.1, Me); 1.47 (*s*, ^{t}Bu); 1.54–1.84 (*m*, 2 CH_2); 2.25–2.41 (*m*, CH_2); 2.46–2.55 (*m*, H–C(5)); 2.94–3.07 (*m*, H–C(3a)); 3.64–3.75 (*m*, CH); 4.16–4.31 (*m*, CH_2O, H–C(4)); 5.06–5.20 (*m*, H–C(6a), NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.4; 12.5; 14.5; 24.4; 25.9; 28.6; 31.6; 36.9; 41.0; 45.6; 52.1; 57.1; 61.6; 62.9; 83.7; 155.4; 160.8. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.92, H 8.76, N 6.7.58.

*Ethyl (3a*R**,5*S**,6*S**,6a*R**)-6-{[(*tert*-Butoxy)carbonyl]amino}-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,2]oxazole-5-carboxylate* (**17**). Yellowish oil. Yield: 6%. R_f (hexane/AcOEt) 0.52. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.21–1.33 (*m*, 3 Me); 1.46 (*s*, ^{t}Bu); 1.51–2.20 (*m*, 2 CH_2); 2.32–2.46 (*m*, CH_2); 2.93–3.07 (*m*, H–C(5)); 3.44–3.54 (*m*, H–C(3a)); 4.01–4.24 (*m*, CH, CH_2O); 4.28–4.40 (*m*, H–C(6)); 4.87–4.92 (*m*, H–C(6a)); 5.64–5.80 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.5; 11.2; 14.5; 23.9; 26.2; 30.0; 31.4; 35.9; 42.1; 44.9; 52.2; 56.9; 59.6; 62.9; 85.0; 155.4; 161.4. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.91, H 8.76, N 7.61.

*Ethyl (3a*S**,5*R**,6*S**,6a*R**)-6-{[(*tert*-butoxy)carbonyl]amino}-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*][1,2]oxazole-5-carboxylate* (**19**). White solid. Yield: 50%. R_f (hexane/AcOEt) 0.38. M.p. 95–96°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89–1.00 (*m*, 2 Me); 1.29 (*t*, *J* = 7.1, Me); 1.46 (*s*, ^{t}Bu); 1.55–1.74 (*m*, 2 CH_2); 1.97–2.04 (*m*, 1 H of CH_2); 2.14–2.31 (*m*, 1 H of CH_2, H–C(5)); 2.38–2.49 (*m*, H–C(3a)); 3.62–3.73 (*m*, CH); 4.09–4.34 (*m*, H–C(6), CH_2O); 4.85–4.91 (*m*, H–C(6a)); 5.19–5.26 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.5; 11.6; 13.6; 23.6; 25.3; 27.8; 29.9; 39.8; 46.4; 50.9; 59.5; 60.6; 79.0; 82.5; 154.6; 162.4; 172.2. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.95, H 8.74, N 7.59.

*Ethyl (1*R**,2*S**,3*S**,4*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}-2-ethylbutyl)-4-hydroxycyclopentanecarboxylate* (**20**). White solid. Yield: 53%. R_f (hexane/AcOEt) 0.26. M.p. 99–100°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80–0.93 (*m*, 2 Me); 1.24–1.67 (*m*, 2 ^{t}Bu, CH_2); 1.97–2.21 (*m*, 1 H of CH_2, H–C(1), H–C(3)); 3.31–3.40 (*m*, CH); 3.77–3.89 (*m*, CH); 4.12–4.28 (*m*, H–C(2), CH_2O); 4.40–4.52 (*m*, H–C(4)); 5.28–5.38 (br. *s*, NH); 5.80–5.90 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.6; 9.9; 13.7; 20.8; 21.4; 27.9; 28.0; 36.5; 43.0; 43.66; 50.1; 50.2; 50.4; 60.4; 73.4; 79.2; 79.5; 155.1; 157.2; 175.1. ESI-MS: 495 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 61.01, H, 9.39, N, 5.94.

*Ethyl (1*R**,2*S**,3*S**,4*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*R**)-1-{[(*tert*-butoxy)carbonyl]-amino}-2-ethylbutyl)-4-hydroxycyclopentanecarboxylate* (**21**). White solid. Yield: 27%. R_f (hexane/AcOEt) 0.53. M.p. 197–198°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90–1.03 (*m*, 2 Me); 1.08–1.24 (*m*, 1 H of CH_2); 1.29 (*t*, *J* = 7.2, Me); 1.38–1.59 (*m*, 2 ^{t}Bu, CH_2); 1.83–1.95 (*m*, 1 H of CH_2); 1.97–2.21 (*m*, CH_2); 3.51–3.65 (*m*, H–C(1)); 3.89–3.99 (*m*, CH); 4.02–4.73 (*m*, CH, CH_2O, H–C(2), H–C(3), H–C(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.4; 11.5; 14.0; 21.2; 22.7; 27.9; 27.94; 35.0; 41.1; 46.1; 50.6; 51.9; 54.2; 50.2; 71.7; 78.9; 79.8; 154.1; 157.2; 174.0. ESI-MS: 495 ($[M+Na]^+$). Anal. calc. for: $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 60.98, H 9.40, N 5.91.

*Ethyl (1*R**,2*S**,3*R**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}-2-ethylbutyl)-3-hydroxycyclopentanecarboxylate* (**22**). Yellowish oil. Yield: 58%. R_f (hexane/AcOEt) 0.47. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90–1.01 (*m*, 2 Me); 1.09–1.34 (*m*, Me, 2 CH_2); 1.46 (*s*, 2 ^{t}Bu); 1.92–2.30 (*m*, CH_2, H–C(1)); 2.76–2.88 (*m*, H–C(4)); 2.94–3.02 (*m*, CH); 3.92–4.03 (*m*, CH); 4.06–4.31 (*m*, H–C(2), H–C(3), CH_2O); 4.35–4.44 (br. *s*, NH); 5.07–5.19 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.0; 12.0; 14.3; 21.0; 24.3; 26.2; 27.0; 28.4; 44.3; 45.4; 48.0; 51.6; 58.8; 63.0; 73.8; 80.0;

127.0; 142.0; 153.7; 158.1. ESI-MS: 474 ($[M+1]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 60.97, H 9.39, N 5.94.

*Ethyl (1*R**,2*S**,3*R**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*R**)-1-{[(*tert*-butoxy)carbonyl]-amino}-2-ethylbutyl)-3-hydroxycyclopentanecarboxylate* (**23**). White solid. Yield: 20%. R_f (hexane/AcOEt) 0.35. M.p. 137–138°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89–1.00 (*m*, 2 Me); 1.29 (*t*, *J* = 7.1, Me); 1.40–1.72 (*m*, 2 ^{t}Bu, 4 CH_2); 1.96–2.52 (*m*, CH_2, H–C(1), H–C(4), CH); 3.60–3.76 (*m*, CH); 4.07–4.42 (*m*, H–C(2), CH_2O, H–C(3)); 4.84–4.93 (br. *s*, NH); 5.16–5.30 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.5; 11.9; 13.7; 21.2; 22.6; 25.2; 27.9; 27.9; 44.3; 44.7; 46.3; 50.9; 58.8; 60.3; 74.2; 79.1; 126.9; 142.0; 154.9; 156.3. ESI-MS: 474 ($[M+1]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 61.01, H 9.36, N 5.92.

*Ethyl (1*R**,2*R**,3*S**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}ethyl)-4-fluorocyclopentanecarboxylate* (**24a**). White solid. Yield: 24%. R_f (hexane/AcOEt) 0.56. M.p. 114–115°. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23 (*d*, *J* = 6.9, Me); 1.27–1.33 (*m*, Me); 1.43–1.49 (*m*, 2 ^{t}Bu); 2.11–2.42 (*m*, CH_2, H–C(1)); 3.00–3.08 (*m*, H–C(3)); 4.41–4.28 (*m*, NH, CH, CH_2O); 4.83–5.09 (*m*, H–C(4), H–C(2)); 5.58–5.67 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.5; 19.6; 28.8; 34.8; 34.9; 45.2; 46.1; 52.2; 55.9; 56.1; 61.3; 79.1; 79.8; 95.9; 152.8; 173.5. ESI-MS: 419 ($[M+1]^+$). Anal. calc. for: $C_{20}H_{35}FN_2O_6$: C 57.40, H 8.43, N 6.69; found: C 57.43, H 8.42, N 5.67.

*Ethyl (1*R**,2*R**)-2-{[(*tert*-butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]amino}-ethyl)cyclopent-3-ene-1-carboxylate* (**25a**). White solid. Yield: 45%. R_f (hexane/AcOEt) 0.52. M.p. 83–84°. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26–1.33 (*m*, 2 Me); 1.42–1.50 (*m*, 2 Me_3C); 2.41–2.52 (*m*, 1 H of CH_2); 2.75–2.86 (*m*, 1 H of CH_2); 3.36–3.45 (*m*, H–C(1)); 4.12–4.22 (*m*, CH_2O); 4.34 (br. *s*, NH); 4.70–5.08 (*m*, NH, CH, H–C(2)); 5.65 (*s*, H–C(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.6; 21.2; 28.7; 28.8; 33.3; 45.7; 47.7; 57.4; 61.0; 79.9; 121.4; 126.2; 155.5; 158.5; 172.9. ESI-MS: 399 ($[M+1]^+$). Anal. calc. for $C_{20}H_{34}N_2O_6$: C 60.28, H 8.60, N 7.03; found: C 60.26, H 8.61, N 7.04.

*Ethyl (1*R**,2*R**,3*S**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-4-fluorocyclopentanecarboxylate* (**24b**). White solid. Yield: 30%. R_f (hexane/AcOEt) 0.74. M.p. 103–104°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.97 (*t*, *J* = 7.3, Me); 1.26–1.33 (*m*, Me); 1.44 –1.50 (*m*, 2 ^{t}Bu); 1.57–1.67 (*m*, CH_2); 2.09–2.45 (*m*, CH_2, H–C(1)); 2.97–3.06 (*m*, H–C(3)); 3.86 (br. *s*, NH); 4.03–4.28 (*m*, CH_2O, H–C(2)); 4.80–5.03 (*m*, CH, H–C(4)); 5.66–5.76 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.5; 13.6; 26.4; 27.9; 34.1; 44.5; 50.9; 51.3; 54.0; 60.5; 78.8; 79.3; 94.5; 95.9; 155.0; 155.9; 173.3. ESI-MS: 434 ($[M+1]^+$). Anal. calc. for $C_{21}H_{37}FN_2O_6$: C 58.31, H 8.62, N 6.48; found: C 58.29, H 8.63, N 6.49.

*Ethyl (1*R**,2*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]amino}pro-pyl)cyclopent-3-ene-1-carboxylate* (**25b**). Brownish oil. Yield: 43%. R_f (hexane/AcOEt) 0.67. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.5, Me); 1.29 (*t*, *J* = 7.2, Me); 1.42–1.50 (*m*, ^{t}Bu); 1.62–1.77 (*m*, CH_2); 2.34–2.53 (*m*, 1 H of CH_2); 2.74–2.90 (*m*, 1 H of CH_2); 3.30–3.45 (*m*, H–C(1)); 4.09–4.28 (*m*, CH, CH_2O); 4.78–5.05 (*m*, 2 NH, H–C(2)); 5.65 (*s*, H–C(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.6; 13.8; 26.6; 27.9; 27.9; 32.5; 46.7; 56.6; 60.2; 79.1; 112.5; 115.4; 117.2; 126.4; 154.8; 171.3; 172.2. ESI-MS: 414 ($[M+1]^+$). Anal. calc. for $C_{21}H_{36}N_2O_6$: C 61.14, H 8.80, N 6.79; found: C 61.13, H 8.82, N 6.80.

*Ethyl (1*R**,2*R**,3*S**,4*S**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]-amino}-2-ethylbutyl)-4-fluorocyclopentanecarboxylate* (**24c**). White solid. Yield: 28%. R_f (hexane/AcOEt) 0.75. M.p. 115–116°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83–0.95 (*m*, 2 Me); 1.17–1.37 (*m*, Me, CH_2); 1.40–1.52 (*m*, 2 ^{t}Bu, CH_2); 2.10–2.38 (*m*, CH_2, CH); 2.46–2.62 (*m*, H–C(1)); 2.98–3.09 (*m*, H–C(3)); 3.79–3.90 (*m*, CH); 4.03–4.29 (*m*, H–C(2), CH_2O); 4.82 (br. *s*, NH); 4.91–5.06 (*m*, H–C(4)); 5.68–5.79 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.5; 10.3; 13.6; 20.8; 21.4; 27.9; 34.0; 41.9; 44.7; 51.1; 51.2; 51.5; 60.5; 78.7; 79.2; 95.3; 96.7; 154.9; 156.0; 173.4. ESI-MS: 475 ($[M+1]^+$). Anal. calc. for $C_{24}H_{43}FN_2O_6$: C 60.74, H 9.13, N 5.90; found: C 60.73, H 9.12, N 5.92.

*Ethyl (1*R**,2*R**)-2-{[(*tert*-Butoxy)carbonyl]amino}-3-((1*S**)-1-{[(*tert*-butoxy)carbonyl]amino}-2-ethylbutyl)cyclopent-3-ene-1-carboxylate* (**25c**). White solid. Yield: 27%. R_f (hexane/AcOEt) 0.61. M.p. 94–95°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.84–1.11 (*m*, 2 Me, CH_2); 1.17–1.36 (*m*, Me, CH_2); 1.39–1.53 (*m*, 2 ^{t}Bu); 2.40–2.53 (*m*, 1 H of CH_2); 2.76–2.89 (*m*, 1 H of CH_2); 3.36–3.47 (*m*, CH); 4.09–4.25 (*m*, CH_2O); 436 (br. *s*, NH); 4.62–5.07 (*m*, CH, NH, H–C(2)); 5.63–5.65 (*m*, H–C(4)). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.2; 12.2; 13.8; 21.1; 22.2; 27.8; 27.9; 32.4; 42.4; 46.7; 50.3; 56.5; 60.1; 78.8; 78.9; 126.5; 143.1;

154.6; 155.2; 172.1. ESI-MS: 455 ($[M+1]^+$). Anal. calc. for $C_{24}H_{42}N_2O_6$: C 63.41, H 9.31, N 6.16; found: C 63.39, H 9.32, N 6.17.

*Ethyl (1*R*,2*S*,3*S*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S*)-1-{[(*tert*-butoxy)carbonyl]-amino}ethyl)-3-fluorocyclopentanecarboxylate* (**26a**). White solid. Yield: 26%. R_f (hexane/AcOEt) 0.51. M.p. 104–105°. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.17–1.23 (*m*, Me); 1.29 (*t*, *J* = 7.2, Me); 1.44–1.49 (*m*, 2 ^{t}Bu); 2.09–2.24 (*m*, 1 H of CH_2); 2.27–2.58 (*m*, 1 H of CH_2, H–C(1)); 2.69–2.94 (*m*, H–C(4)); 3.69–3.89 (*m*, CH); 4.09–4.25 (*m*, CH_2O, H–C(2)); 4.26–4.43 (br. *s*, NH); 4.65–5.00 (*m*, NH, H–C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.7; 15.5; 27.9; 33.5; 36.6; 46.5; 48.1; 50.8; 51.5; 51.7; 60.6; 79.2; 103.6; 105.0; 154.8; 172.6. ESI-MS: 419 ($[M+1]^+$). Anal. calc. for $C_{20}H_{35}FN_2O_6$: C 57.40, H 8.43, N 6.69; found: C 57.41, H 8.41, N 6.70.

*Ethyl (1*R*,4*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S*)-1-{[(*tert*-butoxy)carbonyl]amino}-ethyl)cyclopent-2-ene-1-carboxylate* (**27a**). White solid. Yield: 48%. R_f (hexane/AcOEt) 0.47. M.p. 129–130°. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.18–1.3 (*m*, Me); 1.26–1.33 (*m*, Me); 1.45–1.48 (*m*, 2 ^{t}Bu); 2.29–2.49 (*m*, H–C(1)); 2.57–2.79 (*m*, CH_2); 2.81–2.91 (*m*, H–C(4)); 3.70–3.87 (*m*, NH); 4.15–4.25 (*m*, CH_2O, CH); 4.92–5.01 (*m*, NH); 5.45–5.47 (*m*, H–C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.7; 19.4; 27.9; 36.77; 44.9; 46.7; 46.6; 50.7; 60.4; 78.0; 79.2; 124.7; 148.3; 154.7; 167.8. ESI-MS: 399 ($[M+1]^+$). Anal. calc. for $C_{20}H_{34}N_2O_6$: C 60.28, H 8.60, N 7.03; found: C 60.30, H 8.59, N 7.02.

*Ethyl (1*R*,2*S*,3*S*,4*S*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S*)-1-{[(*tert*-butoxy)carbonyl]-amino}propyl)-3-fluorocyclopentanecarboxylate* (**26b**). Brownish oil. Yield: 15%. R_f (hexane/AcOEt) 0.57. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89–1.02 (*m*, Me); 1.25–1.33 (*m*, Me); 1.44–1.50 (*m*, 2 ^{t}Bu); 1.64–1.80 (*m*, CH_2); 2.23–3.06 (*m*, CH_2, H–C(1), CH); 3.49–3.72 (*m*, H–C(4)); 4.14–4.25 (*m*, CH_2O); 4.29–4.54 (*m*, H–C(2)); 4.57–4.82 (*m*, H–C(3)); 4.97 (br. *s*, NH); 5.13 (br. *s*, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.9; 13.7; 22.7; 27.9; 36.8; 47.9; 49.7; 52.9; 53.7; 57.3; 57.5; 60.5; 79.1; 103.8; 105.2; 154.3; 155.8. ESI-MS: 433 ($[M+1]^+$). Anal. calc. for $C_{21}H_{37}FN_2O_6$: C 58.31, H 8.62, N 6.48; found: C 58.30, H 8.61, N 6.50.

*Ethyl (1*R*,4*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S*)-1-{[(*tert*-butoxy)carbonyl]amino}pro-pyl)cyclopent-2-ene-1-carboxylate* (**27b**). White solid. Yield: 39%. R_f (hexane/AcOEt) 0.48. M.p. 121–122°. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88–1.01 (*m*, Me); 1.24–1.33 (*m*, Me); 1.47 (*s*, 2 ^{t}Bu); 1.61–1.90 (*m*, CH_2); 2.09–2.35 (*m*, 1 H of CH_2); 2.53–2.75 (*m*, 1 H of CH_2); 2.77–2.92 (*m*, H–C(1)); 4.07–4.25 (*m*, H–C(4), CH_2O); 4.47 (br. *s*, NH); 4.56–4.87 (*m*, CH); 4.93–5.05 (*m*, NH); 5.45–5.47 (*m*, H–C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.8; 13.7; 22.6; 26.1; 27.9; 50.6; 51.5; 57.3; 60.5; 79.0; 103.8; 105.2; 124.6; 154.6; 155.8; 172.7. ESI-MS: 413 ($[M+1]^+$). Anal. calc. for $C_{21}H_{36}N_2O_6$: C 61.14, H 8.80, N 6.79; found: C 61.15, H 8.78, N 6.80.

*Ethyl (1*R*,4*R*)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-((1*S*)-1-{[(*tert*-butoxy)carbonyl]amino}-2-ethylbutyl)cyclopent-2-ene-1-carboxylate* (**27c**). Yellowish oil. Yield: 58%. R_f (hexane/AcOEt) 0.48. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85–1.17 (*m*, 2 Me, CH_2); 1.23–1.39 (*m*, Me, CH_2); 1.46 (*s*, 2 ^{t}Bu); 1.58–1.68 (*m*, CH_2); 2.41–2.90 (*m*, CH, H–C(1), CH); 3.51–3.61 (*m*, H–C(4)); 4.07–4.22 (*m*, CH_2O); 4.37 (br. *s*, NH); 4.49 (br. *s*, NH); 5.63–5.64 (*m*, H–C(3)). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.8; 11.2; 13.7; 21.5; 22.6; 27.8; 27.9; 34.4; 43.1; 50.2; 52.0; 57.11; 60.4; 78.5; 79.1; 103.2; 105.5; 153.9; 155.8; 171.7. ESI-MS: 455 ($[M+1]^+$). Anal. calc. for $C_{24}H_{42}N_2O_6$: C 63.41, H 9.31, N 6.16; found: C 63.44, H 9.30, N 6.14.

X-Rray Crystallographic Studies. Crystallographic data for the compounds **11** and **20** were collected with *Agilent Supernova* diffractometer equipped with *Atlas* area detector using CuK_α radiation (λ = 1.54184 Å). Empirical absorption correction, using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm, was applied for both compounds with CrysAlisPro program package [9]. The structures were solved by direct methods using SIR97 [10] program, and full-matrix, least-squares refinements on F^2 were performed using the SHELXL-97 [11] program. Molecular structure figures were drawn with Diamond3 program [12]. Selected crystallographic data collected in CCDC-902350 and -902351 contain the supplementary crystallographic data for **11** and **20**. These data can be obtained free of charge *via* ttp://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

REFERENCES

[1] a) F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181; b) L. Kiss, E. Forró, F. Fülöp, 'Synthesis of carbocyclic β-amino acids', in 'Amino Acids, Peptides and Proteins in Organic Chemistry', Vol. 1, Ed. A. B. Hughes, Wiley, Weinheim, 2009, p. 367; c) L. Kiss, F. Fülöp, *Synlett* **2010**, 1302; d) D. Seebach, A. K. Beck, S. Capone, D. Deniau, U. Grošelj, E. Zass, *Synthesis* **2009**, 1; e) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1; f) D. J. Ramón, G. Guilenna, D. Seebach, *Helv. Chim. Acta* **1996**, *79*, 875; g) Z. Hameršak, M. Roje, A. Avdagić, V. Šunjić, *Tetrahedron: Asymmetry* **2007**, *18*, 635; h) S. K. Pandey, G. F. Jogdand, J. C. A. Oliveira, R. A. Mata, P. R. Rajamohanan, C. V. Ramana, *Chem.–Eur. J.* **2011**, *17*, 12946.

[2] T. A. Martinek, F. Fülöp, *Eur. J. Biochem.* **2003**, *270*, 3657; E. Torres, C. Acosta-Silva, F. Rúa, Á. Álvarez-Larena, T. Parella, V. Branchadell, R. M. Ortuño, *Tetrahedron* **2009**, *65*, 5669; D. Fernández, E. Torres, F. X. Avilés, R. M. Ortuño, J. Vendrell, *Bioorg. Med. Chem.* **2009**, *17*, 3824; C. Fernandes, E. Pereira, S. Faure, D. J. Aitken, *J. Org. Chem.* **2009**, *74*, 3217; O. Roy, S. Faure, D. J. Aitken, *Tetrahedron Lett.* **2006**, *47*, 5981; F. Rúa, S. Boussert, T. Parella, I. Díez-Pérez, V. Branchadell, E. Giralt, R. M. Ortuño, *Org. Lett.* **2007**, *9*, 3643; V. D'Elia, H. Zwicknagl, O. Reiser, *J. Org. Chem.* **2008**, *73*, 3262; C. Fernandes, S. Faure, E. Pereira, V. Théry, V. Declerck, R. Guillot, D. J. Aitken, *Org. Lett.* **2010**, *12*, 3606; F. Fülöp, T. A. Martinek, G. K. Tóth, *Chem. Soc. Rev.* **2006**, *35*, 323; S. Celis, E. Gorrea, P. Nolis, O. Illa, R. M. Ortuño, *Org. Biomol. Chem.* **2012**, *10*, 861; T. A. Martinek, F. Fülöp, *Chem. Soc. Rev.* **2012**, *41*, 687; E. Gorrea, P. Nolis, E. Torres, E. Da Silva, D. B. Amabilino, V. Branchadell, R. M. Ortuño, *Chem.–Eur. J.* **2011**, *17*, 4588.

[3] A. J. Oakley, S. Barrett, T. S. Peat, J. Newman, V. A. Streltsov, L. Waddington, T. Saito, M. Tashiro, J. L. McKimm-Breschkin, *J. Med. Chem.* **2010**, *53*, 6421; W. J. Lü, Y. L. Chen, W. P. Ma, X. Y. Zhang, F. Luan, M. C. Liu, X. G. Chen, Z. D. Hu, *Eur. J. Med. Chem.* **2008**, *43*, 569; P. Chand, P. L. Kotian, A. Dehghani, Y. El-Kattan, T.-H. Lin, T. L. Hutchison, Y. S. Babu, S. Bantia, A. J. Elliott, J. A. Montgomery, *J. Med. Chem.* **2001**, *44*, 4379; P. Chand, Y. S. Babu, S. Bantia, S. Rowland, A. Dehghani, P. L. Kotian, T. L. Hutchison, S. Ali, W. Brouillette, Y. El-Kattan, T.-H. Lin, *J. Med. Chem.* **2004**, *47*, 1919; X. Yi, Z. Guo, F. M. Chu, *Bioorg. Med. Chem.* **2003**, *11*, 1465; P. Chand, S. Bantia, P. L. Kotian, Y. El-Kattan, T.-H. S. Lin, Y. S. Babu, *Bioorg. Med. Chem.* **2005**, *13*, 4071; Y. Cui, Z. Jiao, J. Gong, Q. Yu, X. Zheng, J. Quan, M. Luo, Z. Yang, *Org. Lett.* **2010**, *12*, 4; X. Yi, Z. Guo, F. M. Chu, *Bioorg. Med. Chem.* **2003**, *11*, 1465.

[4] N. C. Yoder, K. Kumar, *Chem. Soc. Rev.* **2002**, *31*, 335; R. I. Mathad, B. Jaun, O. Flögel, J. Gardiner, M. Löweneck, J. D. C. Codée, P. H. Seeberger, D. Seebach, M. K. Edmonds, F. H. M. Graichen, A. D. Abell, *Helv. Chim. Acta* **2007**, *90*, 2251; X.-L.Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711; A. Sutherland, C. L. Willis, *Nat. Prod. Rep.* **2000**, *17*, 621; R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727; A. E. Sorochinsky, V. A. Soloshonok, *J. Fluorine Chem.* **2010**, *131*, 127; Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem.–Eur. J.* **2010**, *16*, 779; S. Capone, I. Kieltsch, O. Flögel, G. Lelais, A. Togni, D. Seebach, *Helv. Chim. Acta* **2008**, *91*, 2035; D. F. Hook, F. Gessier, C. Noti, P. Kast, D. Seebach, *ChemBioChem* **2004**, *5*, 691; C. Jäckel, W. Seufert, S. Thust, B. Koksch, *ChemBioChem* **2004**, *5*, 717; J. L. Aceña, A. E. Sorochinsky, V. A. Soloshonok, *Synthesis* **2012**, *44*, 1591; M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye, B. Koksch, *Chem. Soc. Rev.* **2012**, *41*, 2135; V. S. Yarmolchuk, P. K. Mykhailiuk, I. V. Komarov, *Tetrahedron Lett.* **2011**, *52*, 1300; I. Yamamoto, M. J. T. Jordan, N. Gavande, M. R. Doddareddy, M. Chebib, L. Hunter, *Chem. Commun.* **2012**, *48*, 829.

[5] J. Luis Acena, A. Simon-Fuentes, S. Fustero, *Curr. Org. Chem.* **2010**, *14*, 928; S. Fustero, J. F. Sanz-Cervera, J. L. Acena, M. Sanchez-Rosello, *Synlett* **2009**, 525; K. Mikami, S. Fustero, M. Sánchez-Roselló, J. L. Aceña, V. Soloshonok, A. Sorochinsky, *Synthesis* **2011**, 3045.

[6] a) L. Kiss, E. Forró, S. Fustero, F. Fülöp, *Eur. J. Org. Chem.* **2011**, 4993; b) L. Kiss, E. Forró, S. Fustero, F. Fülöp, *Org. Biomol. Chem.* **2011**, *9*, 6528 c) J. Mittendorf, F. Kunisch, M. Matzke, H.-C. Militzer, A. Schmidt, W. Schönfeld, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433; d) S. Fustero, J. F. Sanz-Cervera, J. Piera, M. Sánchez-Roselló, G. Chiva, A. Simón-Fuentes, *J. Fluorine Chem.* **2004**, *125*, 621; e) S. Fustero, M. Sánchez-Roselló, J. L. Aceña, B. Fernandez, A. Asensio, J. F. Sanz-Cervera, C.

del Pozo, *J. Org. Chem.* **2009**, *74*, 3414; f) S. Fustero, M. Sánchez-Roselló, J. F. Sanz-Cervera, J. L. Aceña, C. del Pozo, B. Fernández, A. Bartolomé, A. Asensio, *Org. Lett.* **2006**, *8*, 4633.
[7] M. Nonn, L. Kiss, R. Sillanpää, F. Fülöp, *Beilstein J. Org. Chem.* **2012**, *8*, 100.
[8] a) L. Kiss, M. Nonn, E. Forró, R. Sillanpää, F. Fülöp, *Tetrahedron Lett*. **2009**, *50*, 2605; b) M. Nonn, L. Kiss, E. Forró, Z. Mucsi, F. Fülöp, *Tetrahedron* **2011**, *67*, 4079.
[9] R. C. Clark, J. S. Reid, *Acta Cryst., Sect. A* **1995**, *51*, 887; CrysAlis PRO, 2012, Agilent Technologies, Yarnton, England.
[10] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[11] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112.
[12] Diamond – Crystal and Molecular Structure Visualization, Crystal Impact, K. Brandenburg and H. Putz, Postfach 1251, D-53002 Bonn.

Received September 17, 2012